

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Merrill et al.
Appl. No. : 10/659,711
Filed : September 11, 2003
For : ANTIBACTERIAL THERAPY
WITH BACTERIOPHAGE
GENOTYPICALLY MODIFIED
BY GENETIC ENGINEERING TO
DELAY INACTIVATION BY
THE HOST DEFENSE SYSTEM
Examiner : Snyder, Stuart
Group Art Unit : 1648

DECLARATION UNDER 37 CFR 1.132 OF CARL R. MERRIL, M.D.

I, Carl R. Merrill, M.D., do hereby declare:

1. I am a named inventor of the above-identified application. A true and correct copy of my Curriculum Vitae is attached as Exhibit A.
2. This declaration is to discuss the issues that would be the most important to address in order to overcome the enablement rejection, i.e., the state of the art at the April 1994 time of filing with regard to predictability of altering the phage surface to diminish complement activation.
3. The invention solves the problem in the prior art of the use of bacteriophage to fight infections caused by bacteria. We reasoned that one explanation for bacteriophage not always working was because the viruses were inactivated by the host defense system. To solve this problem, we developed a technology to produce bacteriophage that may be serially passaged or genetically modified to delay inactivation by the host defense system.
4. Using the serial passage technology, we developed long-circulating bacteriophage that are greatly superior to wildtypes in terms of rescuing animals from otherwise fatal infections. These results were published as Merrill et al., Proc Natl Acad Sci USA 93: 3188 (1996). We patented this embodiment as U.S. Patent No. 5,688,501, to mention one.

5. Using the genetic engineering technique, we proceeded to demonstrate that the mutation in the major phage capsid (E) protein, which resulted in the change of the acidic amino acid glutamate to the basic amino acid lysine at residue 158, conferred the "long-circulating" phenotype. These results were published as Vitiello et al., *Virus Res* 114: 101 (2005). Thus we were able to duplicate the solution to the host defense problem afforded by the serial passage technique with the genetic engineering technology.

6. As we proposed in our patent application: We elucidated that one of the ways to delay inactivation by the host defense system is to engineer a phage to express molecules that antagonize one or more of the complement components. It was known that viruses that infect animals encode inhibitors of complement activation to evade host immune responses. E.g., Isaacs et al., *Proc Natl Acad Sci USA* 89: 628 (1992). Bacteriophage did not evolve to express immune response genes like poxviruses because they infect bacteria not animals.

7. As we proposed in our patent application: Complement components fix to bacteriophages, and these bacteriophages then adhere to certain white blood cells (such as macrophages) that express complement receptors. Numerous peptides have been synthesized that antagonize the functions of the various complement components. See, e.g., Lambris, J. D. et al, "Use of synthetic peptides in exploring and modifying complement reactivities" in *Activators and Inhibitors of Complement*, ed. R. Sim, Kluwer Academic Publishers, Boston, 1993. Lambris et al. (op.cit.) cite "a series of synthetic peptides spanning the convertase cleavage site in C3 (that are) found to inhibit complement activation by both the classical and alternative pathways". Among the peptides cited is a six amino acid peptide (LARSNL, residues 746-751 of C3) that "inhibits both pathways equally well".

8. As we proposed in our patent application: In one method of genetically engineering such a phage, a fusion protein is obtained, wherein the peptide will be bound to the carboxyl end of the surface protein of interest See, e.g., Sambrook, J., Fritsch, E., and Maniatis, T.: *Molecular Cloning. A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. This construct is made by cloning the gene for the phage surface protein into a plasmid vector system, and then cloning the oligonucleotide for the peptide

of interest into this carrying vector by in-frame fusion at the 3'-end of the gene for the surface protein. This fusion of the gene for the phage surface protein with the oligonucleotide for the complement-antagonizing peptide would then be incorporated into the phage of interest by the in vivo generalized recombination system in the host bacteria for the phage of interest. Phage whose genomic sequence is already completely known, and phage whose genomic sequence is unknown or partially unknown can be used in the present invention.

9. As we proposed in our patent application at Example 4: Genetic engineering of phage to express molecules that antagonize the host defense system, thereby enabling the phage to delay inactivation by the host defense system may be exemplified as follows.

Part 1. Making the Fusion Protein.

Step 1. A double-stranded DNA encoding the complement antagonizing peptide LARSNL is synthesized on an automated oligonucleotide synthesizer using standard techniques.

Step 2. The gene for the phage coat surface protein of interest (see Part 2, below) is cloned into a plasmid vector system, by techniques known in the art. The oligonucleotide that has been prepared in Step 1 is cloned into the plasmid vector system by in-frame fusion at the 3'-end of the gene for the surface protein.

Step 3. The fusion gene is then incorporated into a phage by the in vivo generalized recombination system in the host bacteria for the phage. The phage then expresses the fusion protein on its surface.

Part 2. Selecting phage coat surface proteins for fusion with the peptide/protein of interest.

A. Incorporating the gene for the complement-antagonizing peptide into a phage whose genome is well characterized.

The orfx gene, which encodes a carboxy-terminal tail protein of lambda coliphage, is one for which it is known that foreign nucleotide sequences can be introduced without there being disruption of the structure or function of the phage. Montag et al., J Bacteriol 171: 4378 (1989).

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The tail surface protein expressed by the orfx gene is made into a fusion protein with the complement-antagonizing peptide, by the plasmid vector method described in Part 1 above.

B. Incorporating a gene for a complement-antagonizing peptide into a phage whose genome is not well characterized.

Step 1. Selection of the phage surface protein to be fused with the complement-antagonizing peptide:

a) Isolation of phage coat surface proteins and preparation of antibodies thereto:

(1) Samples of the phage of interest are broken up in 0.1% SDS detergent for 2 minutes at 95°C. The mixture is cooled and placed in 9M urea, and is then separated by high resolution 2D gel electrophoresis. The protein fragments are then isolated from the gel, and processed as described below.

(2) Samples of the protein fragments from the gel are injected into animals to produce either polyclonal or monoclonal antibodies.

(3) Antibodies are isolated and then marked with uranium. These marked antibodies are reacted against whole phage. The marker pinpoints precisely those proteins on the surface of the phage to which the antibodies have bound through visualization by electron microscopy. See, e.g., K. Williams and M. Chase, ed., Methods In Immunology and Immunochemistry, Vol.1, 1967, Academic Press. Antibodies directed against a surface protein extending outward from the surface of the virus are retained for further use.

b) Preparation of phage restriction fragments:

The genome of the phage is cut by restriction enzymes, and the resulting restriction fragments are cloned into expression vector plasmids. Each of these plasmids expresses its corresponding protein, creating a pool of expressed proteins.

c) Reacting the expressed proteins with the marked antibodies:

The antibodies directed against a surface protein extending outward from the surface of the virus are reacted against the proteins expressed by the plasmid vectors.

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d) Correlating coat protein antibodies to the plasmid vectors that express the genes for those coat proteins:

The reaction of a marked antibody with an expressed protein pinpoints the expression plasmid whose enclosed restriction fragment expresses the particular protein. Thus, the genomic fragment encoding each coat surface protein is determined using the marked antibodies.

e) Determining that the gene in its entirety has been obtained:

The restriction fragments containing a gene for a surface protein are micro-sequenced by the Sanger technique to determine

(1) the precise amino acid sequence of the coat surface proteins;

(2) the presence of a start and a stop signal (indicating that the gene in its entirety has been obtained); and

(3) the presence of either a C-terminal or an N-terminal amino acid.

Step 2. Fusing the candidate phage surface protein with the complement-antagonizing peptide of interest:

a) Preparing the coat protein gene for fusion:

The gene for a surface protein is contained in its plasmid expression vector. The oligonucleotide for the complement-antagonizing peptide is spliced into this plasmid expression vector by in-frame fusion at the 3'-end of the coat surface protein.

b) Incorporating the fusion gene into the phage of interest:

The fusion gene is incorporated into the phage by the in vivo generalized recombination system in the host bacteria for the phage.

c) Demonstrating that the phage expresses the fusion protein:

The phage is incubated with a corresponding heavy metal-marked antibody that has been raised against the coat surface protein. The marker is detected on the phage by electron microscopy only if the phage has expressed that fusion protein on its surface. See, e.g., K.

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Williams and M. Chase, Methods In Immunology and Immunochemistry, Vol.1, 1967, Academic Press.

10. As we proposed in our patent application at Example 5: Demonstration that the genetically engineered phage delay inactivation by the host defense system, compared to wild-type phage is exemplified as follows.

Two groups of mice are injected with phage as specified below:

Group 1: The experimental group receives an IV injection consisting of 1×10^{12} of the genetically modified phage, suspended in 0.5 cc of sterile normal saline.

Group 2: The control group receives an IV injection consisting of 1×10^{12} of the wild-type phage from which the genetically modified phage were derived, suspended in 5 cc of sterile normal saline.

Both groups of mice are bled at regular intervals, and the blood samples assayed for phage content (by pfu assays) to determine the following:

1) Assays for half-lives of the two phages: For each group of mice, the point in time is noted at which there remains in circulation only half (i.e., 1×10^6) the amount of phage as administered at the outset. The point in time at which half of the genetically modified phage have been eliminated from the circulation is at least 15% longer than the corresponding point in time at which half of the wild-type phage have been eliminated from the circulation.

2) Assays for absolute numbers: For each group of mice, a sample of blood is taken at precisely 1 hour after administration of the phage. The criterion used is that at 1 hour post-injection, pfu assays reveal that the numbers of genetically engineered phage still in circulation in the experimental animal are at least 10% higher than the numbers of wild-type phage still in circulation in the control animal.

11. As we proposed in our patent application at Example 6: Determination that the genetically engineered phage has a greater capacity than wild type phage to prevent lethal infections in mice is exemplified as follows.

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Part 1. Peritonitis Model:

An LD₅₀ dosage of E. coli is administered intraperitoneally (IP) to laboratory mice. The strain of E. coli used is one known to be lysed by the coliphage strain that has been genetically engineered. The treatment modality is administered precisely 20 minutes after the bacteria are injected, but before the onset of symptoms. The treatment modalities consist of the following:

Group 1: The experimental group receives an IP injection consisting of 1×10^{12} of the genetically engineered lambda coliphage suspended in 2 cc of sterile normal saline.

Group 2: A first control group receives an IP injection consisting of 1×10^{12} of the wild-type phage from which the genetically modified phage were developed, suspended in 2 cc of sterile normal saline.

Group 3: A second control group receives an IP injection of sterile normal saline.

Evidence that treatment with the genetically modified phage prevented the development of a lethal event in the peritonitis model is measured by using the following three criteria:

- (1) Survival of the animal;
- (2) Bacterial counts: Samples of peritoneal fluid are withdrawn every 1/2 hour from the three groups of infected mice, and the rate of increase or decrease in E. coli colony counts in the three groups is noted; and
- (3) Phage control: Using the samples of IP fluid withdrawn from the infected mice, the numbers of pfu of the genetically engineered phage versus the numbers of pfu of the wild-type phage are noted.

Part 2. Bacteremia Model:

An LD₅₀ dosage of E. coli is administered intravenously (IV) to laboratory mice, where the strain of E. coli used is known to be lysed by the coliphage strain that was genetically engineered. The treatment modality (see below) is administered precisely 20 minutes after the bacteria are injected, but before the onset of symptoms. The treatment modalities consist of the following:

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Group 1: The experimental group receives an IV injection consisting of 1×10^{12} of the genetically engineered lambda coliphage suspended in 0.5 cc of sterile normal saline.

Group 2: A first control group receives an IV injection consisting of 1×10^{12} of the wild-type phage from which the genetically engineered phage were developed, suspended in 0.5 cc of sterile normal saline.

Group 3: A second control group receives an IV injection of 0.5 cc of sterile normal saline.

Evidence that treatment with the genetically engineered phage prevented the development of a lethal event in the bacteremia model is measured using the following three criteria:

- (1) Survival of the animal;
- (2) Bacterial counts: In the samples of blood that are withdrawn every 1/2 hour from the three groups of infected mice, the absolute numbers as well as the rate of increase or decrease in *E. coli* colony counts is noted, for each of those three groups; and
- (3) Phage counts: In the samples of blood withdrawn from the infected mice, the numbers of pfu of the genetically engineered phage and the numbers of pfu of the wild-type phage are noted.

12. Thus this declaration discusses the issues that would be the most important to address in order to overcome the enablement rejection, i.e., the state of the art at the April 1994 time of filing with regard to predictability of altering the phage surface to diminish complement activation. In sum, the Lambris paper is a representative paper exemplifying the state of the art with regard to peptides that modify complement reactivities foreign to bacteriophages. The Isaacs paper shows that viruses that infect animals encode proteins that inhibit complement activation, thus inhibiting complement activation is compatible with the viability of a virus. The Montag paper is a representative paper exemplifying the state of the art with regard to the display of a foreign peptide on the surface of a phage while preserving infectivity. The conclusion is that altering the phage surface to diminish complement activation was enabled by the patent specification in view of the state of the art at the April 1994 time of filing.

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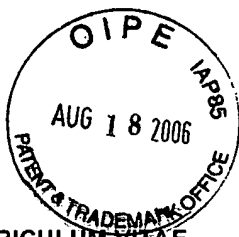
I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Respectfully submitted,

Dated: Aug 9, 2006

By: Carl R. Merrill, M.D.
Carl R. Merrill, M.D.

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CURRICULUM VITAE

March 19, 2006

Name: Carl R. Merrill, M.D.

Date and Place of Birth: December 6, 1936, New York

Citizenship: United States

Marital Status: Married, two sons

Education:

1954-1958 - B.S. (Chemistry), College of William and Mary,
Williamsburg, VA.

1958-1962 - M.D. Georgetown University, School of Medicine,
Washington, DC.

Brief Chronology of Employment:

2005-Present – appointed NIH Scientist Emeritus

2004-2005 - Acting Chief, Laboratory of Genetics, Intramural Research Program, NIMH, NIH

1988-2002 - Chief, Laboratory of Biochemical Genetics, Intramural Research Program, NIMH, NIH
and Chairman of the Surgeon General's Advisory Panel for the P.H.S. Research Officer
Group.

1984-1988 - Chief, Biochemical Genetics Section, Clinical Neurogenetics Branch, NIMH-DIRP,
Bethesda, MD

1969-1984 - Senior Staff, Section on Proteins, Laboratory of General and Comparative Biochemistry,
NIMH-IRP, Bethesda, MD

1965-1969 - Senior Staff, Laboratory of Neurochemistry, NIMH-IRP, Bethesda, MD

1963-1965 - Research Associate, Section on Physical Chemistry, Laboratory of Neurochemistry,
NIMH-IRP, Bethesda, MD

1962-1963 - Intern, U.S. Public Health Service Hospital, Boston, MA

1960-1962 - Medical Student and Student Fellow, Cardio-Pulmonary Physiology Laboratory, Mt. Alto
Veterans Administration Hospital and Department of Medicine, Georgetown University
Medical School, Washington, DC

1958-1959 - Medical Student and Student Fellow, Dept. of Biochemistry, Georgetown University
Medical School, Washington, DC

Recent Research Interests:

My Laboratory's studies employed non-biased approaches, such as high-resolution two-dimensional protein electrophoresis to search for abnormal biochemical pathways and genomic alterations in diseases of unknown etiology, which affect the central nervous system. In these efforts, we developed a new method for the detection of proteins to increase the sensitivity of detection over that of silver staining.

In addition to research on diseases of the central nervous system, my laboratory has returned to an earlier interest in bacterial viruses. The increased prevalence of multidrug resistant bacterial pathogens motivated an attempt to enhance the therapeutic efficacy of bacteriophages. The Laboratory recognized that the therapeutic application of phages as antibacterial agents had been impeded by several factors. The first factor was the failure to recognize the relatively narrow host range of phages in many of the attempts to use phage in antibacterial therapy. A second factor was the failure of early investigators to remove the toxins present in crude phage lysates. A third factor, a lack of appreciation for the capacity of mammalian host defense systems, particularly the organs of the reticuloendothelial system (RES), to remove phage particles from the circulatory system, may have severely reduced the efficiency of parenterally administered phage preparations. To reduce phage elimination by the host defense system, the Laboratory and collaborating researchers developed a serial passage technique in mice to select for phage mutants able to remain in the circulatory system for longer periods of time. By addressing these factors we have developed long-circulating mutants of phage for a number of different bacteria and we have demonstrated that these long-circulating phage mutants have greater capability as antibacterial agents than the corresponding parental strain in animals infected with lethal doses of bacteria. Recently this effort has been extended to vancomycin resistant *Enterococcus faecium*. In these experiments we found that that phage specific for vancomycin resistant *Enterococcus faecium* could rescue mice that were infected by intraperitoneal injection with bacteria. If titers of phage equivalent to the titers of infecting bacteria were given 45 minutes after infection, 100% of the mice were rescued and even when treatment was delayed for 24 hours, when the mice were moribund, 50% could still be rescued.

Major Research Experience:

2002- 2005. As acting Chief of the Laboratory of Genetics and Chief of the Section of Biochemical Genetics, NIMH, efforts were made to explore ways to enhance the sensitivity of protein detection so that protein variations can be studied in the highly heterogeneous brain in normal and disease states. Traditionally protein studies have been performed on samples from brain regions. However, even when such regions are dissected microscopically they often contain numerous cell types, each with different functions and morphology. Our current technology does not permit detection of protein from single cells or even small numbers of cells. To facilitate the development of such technology I established collaborations with chemists and physicists at the National Institute of Science and Technology (NIST). In this collaboration we are using quantum dots as highly sensitive tags for protein and nucleic acid detection. In addition, I continued efforts to develop bacterial viruses as agents for the treatment and diagnosis of bacterial diseases. In this endeavor I received an Intramural Biodefense research grant to work in collaboration with Dr. Sankar Adhya in the NCI on the use of bacteriophage as a defense for *Yersinia pestis* (Plague). Two additional researchers were recruited using contract mechanisms and initial success was made in genetically engineering reporter genes into phage strains that may be of use in these studies. We also developed an isogenic pair of Lambda bacteriophage in which one of the pair has a 16,000 fold greater capacity to remain in a mouse circulatory system 24 hours after injection. We have shown that this difference is due to a single base pair change in the phage genome resulting in the change of a glutamic acid to a lysine at residue 158 of the lambda capsid E protein (one of the major capsid proteins of this virus, which is present in about 450 copies per virion). This isogenic pair of viruses may be useful in studies of the innate immune system and they will provide guidance for the development of more effective antibacterial therapeutic phage strains.

1988 -2002 As Chief of the Laboratory of Biochemical Genetics, NIMH, I initiated studies to develop non-biased approaches to search for abnormal biochemical pathways and genomic alterations in diseases of unknown etiology which affect the central nervous system. These studies involved the use of: high resolution two-dimensional protein electrophoresis to study protein variations and polymorphisms; polymorphic microsatellite markers from genomic sequences and human cDNA libraries; examination of mitochondrial genomic stability by measuring the frequency of mitochondrial DNA deletion mutations and by adapting comparative genomic hybridization technologies to search the genome of somatic tissues (particularly in the CNS) for amplified or deleted genetic elements.

We used highly polymorphic genomic linkage probes, developed in my Laboratory, to search for evidence of a postzygotic somatic mutation, such as chromosomal crossovers, in monozygotic twins discordant for schizophrenia. No evidence of such a postzygotic error was found. However, the approach developed in these efforts may be of use in studying other disorders which display discordancy or in searching for somatic variations in disease states. In addition, we developed over 70 polymorphic microsatellite markers from genomic sequences and human cDNA libraries and we participated in determining the chromosomal assignment of 550 brain expressed genes by the segregation of PCR products in human-rodent somatic cell hybrids and by genetically mapping polymorphic cDNAs using the CEPH reference pedigrees. Currently we are concentrated the Laboratory's efforts on the occurrence of mitochondrial DNA (mtDNA) deletion mutations in specific regions of the brain. In prior studies, generally utilizing less than a dozen clinical samples, mtDNA deletions were reported to increase in specific regions of the brain with aging. However, in our Laboratory's studies we examined brain tissue from 43 age-comparable individuals (between ages 34 and 73) we found 12 fold and 5 fold higher levels of mtDNA deletions in the putamen and the superior frontal gyrus of the cortex respectively, from individuals who had conditions associated with chronic hypoxia when compared with individuals without evidence of such conditions. These findings suggest that conditions associated with chronic hypoxia, and not just aging, should be more closely examined in mitochondrial related pathophysiological conditions of the central nervous system.

In addition to research on diseases of the central nervous system, the laboratory has returned to an earlier interest in bacterial viruses. The increased prevalence of multidrug resistant bacterial pathogens motivated us to attempt to enhance the therapeutic efficacy of bacteriophages. The therapeutic application of phages as antibacterial agents has been impeded by several factors: first, the failure to recognize the relatively narrow host range of phages; second, the presence of toxins in crude phage lysates; and third, a lack of appreciation for the capacity of mammalian host defense systems, particularly the organs of the reticuloendothelial system (RES), to remove phage particles from the circulatory system. In our studies involving bacteremic mice, the problem of the narrow host range of phage was dealt with by using selected bacterial strains and virulent phage specific for them. Toxin levels were diminished by purifying phage preparations. To reduce phage elimination by the host defense system, we developed a serial passage technique in mice to select for phage mutants able to remain in the circulatory system for longer periods of time. The use of toxin-free, bacteria-specific phage strains, combined with the serial passage technique, may provide insights for developing phage into therapeutically effective antibacterial and gene transfer agents which could significantly augment our ability to treat diseases.

1984 - 1988- I Organized the Section on Biochemical Genetics in the Clinical Neurogenetics branch of the NIMH. This section developed and employed high resolution two-dimensional protein electrophoresis to study protein variations and polymorphisms in diseases of the central nervous system. In addition, studies were initiated to determine somatic cell and germline genetic variability in the mitochondrial genome.

- 1979 - 1983- I introduced the use of the silver stains to detect proteins separated by electrophoretic methods. These stains increased our ability to detect proteins by almost 100 fold. We used our newly developed methods to study proteins in genetically manipulated cells. This effort led to elucidation of a model for the translational origin of discoordinate induction of the enzymes of the galactose operon in *E. coli*. The technology was also applied to clinical problems resulting in the discovery of a number of trait-specific protein markers, including two previously unidentified CSF (26kD, pI 5.2 and 29kD, pI 5.1) in patients with Creutzfeldt-Jakob disease (CJD). These proteins have proven to be useful diagnostic aids in CJD.
- 1969 - 1979- I studied the effects of bacterial viruses and their genes in mammalian cells. Galactosemic human cells were infected with lambda virus and lambda viral DNA carrying the bacterial galactose operon. A number of assay systems including DNA-RNA hybridization, gal-transferase assays and ^{14}C -galactose to $^{14}\text{CO}_2$ studies indicated that human cells (from galactosemic individuals, missing gal-transferase activity) could express bacterial gal-transferase activity when they were infected with lambda-gal virus. These experiments also led to the discovery that commercial fetal calf serum (used to grow mammalian cells in culture) is contaminated with bacterial viruses and that many vaccines which utilize fetal calf serum for their manufacture are contaminated with bacterial viruses.
- 1966 - 1969- Following a summer course on bacterial viruses at Cold Spring Harbor, I began studies on the molecular biology of the bacterial viruses. These studies included initiation of studies on the basis of site specific recombination and the development of methods for studying recombinant DNA.
- 1963 - 1966- I served as a Research Associate in the Section on Physical Chemistry, Laboratory of Neurochemistry, NIMH. My main research efforts involved the development of methods for the sequence determination of nucleic acids. I developed computer programs to reconstruct primary nucleic acid sequences from fragment data obtained by chemical analysis. This effort was extended to the analysis of the one of the first nucleic acids sequenced, alanine t-RNA. A number of ambiguities were detected in the published data which may have been due to heterogeneity in the "purified alanine t-RNA" employed by Holly and his co-workers.
- 1962 - 1963- I participated in research on acid-base problems associated with open heart surgery at both the Boston PHS Hospital and the Peter Bent Brigham Hospital during my medical internship.
- 1958 - 1962- During my tenure as a medical student at Georgetown University School of Medicine I was awarded a Public Health Service Research Fellowship in Cardio-Pulmonary Physiology. Research conducted during this fellowship involved a study of the relationship of the partial pressures of oxygen and CO_2 in the circulatory system and central nervous system.

Society Membership:

Alpha Omega Alpha, Honorary Medical Society
American College of Neuropsychopharmacology
American Association for the Advancement of Science
American Electrophoresis Society
American Society for Microbiology
American Society of Human Genetics
Association of Military Surgeons of the United States
Biophysical Society
International Electrophoresis Society
New York Academy of Science
Society for Neuroscience
The Protein Society

Government Committee Appointments:

- 2000- 2003 – Member IRB for the NIAAA, Intramural Research Program.
- 1996-1997 - Chairman, Commissioned Corps of the PHS Human Resources Management Model Work Group.
- 1994-1995 - Chairman, Surgeon General's workgroup on Recruitment for the Commissioned Corps of the PHS.
- 1991-1996 - Chairman, NIMH, Extramural Research Promotion and Tenure Review Committee.
- 1991-1993 - Member Surgeon General's Workgroup on Force Management of the Commissioned Corps of the PHS.
- 1991-1993 - Member Surgeon General's Workgroup on Commissioned Corps billets.
- 1989-1998 - Chairman, Surgeon General's Advisory Panel for the Research Officer Group, U.S. Public Health Service.
- 1988-1993 - ADAMHA Representative to the Office of the Surgeon General.
- 1988-1993 - Member, NIMH Intramural Research Promotion and Tenure Review Committee.
- 1988-1992 - NIMH Representative to the NIH Advisory Committee on Computer Usage.
- 1987-1992 - NIMH Commissioned Officer Liaison Representative to ADAMHA Commissioned Corps Revitalization.
- 1986-1988 - Chairman, NIMH, IRP, Cost Reduction Committee.
- 1982-1985 - Chairman, NIMH, Scientific Directors Intramural Research Program Seminar Series
- 1981-1984 - Member NIMH Clinical Review Panel for Human Research Protocols
- 1978-1981 - NIMH Representative on the NIH Biohazard Committee
- 1976-1984 - NIMH Representative on the NIH Biosafety Committee

Teaching Experience:

- 1974 - Present - Adjunct professor in Biochemistry, Medical School, George Washington University.
- 1971-1990 - Organized and taught a Biochemical Genetics Course in the Graduate Departments of Biochemistry and Genetics at George Washington University.
- 1969 - present - Adjunct professor in Genetics, George Washington University.
- 1996 - 2000 - Member of the Graduate Faculty at the University of Maryland.

Military Service:

1954-1958 - U.S. Army R.O.T.C.
1958-1962 - U.S. Army Reserve
1962-1998 - Commissioned Corps, P.H.S.

P.H.S. Commissioned Corps and other Government Awards:

1. *United States Dept. of Commerce Inventors Award* - 1983.
2. PHS Commissioned Corps *Commendation Medal* "For the development of silver staining and protein mapping methodologies which have opened up significant new opportunities in the study of genetic diseases". 1984.
3. PHS Commissioned Corps *Unit Commendation Ribbon* "For participation and service as chairman of an ADAMHA workgroup on the revitalization of the PHS Commissioned Corps". 1988.
4. PHS Commissioned Corps *Outstanding Service Medal* "For Leadership in the development of new biochemical methods for the investigation of human diseases". 1988.
5. PHS Commissioned Corps *Surgeon General's Exemplary Service Medal*, from Surgeon General, Dr. Koop, "For Initiating the Organization of the Research Officer Group for doctoral level researchers in the Corps". 1989.
6. PHS Commissioned Corps *Unit Commendation Ribbon* "For the development of billets for the Research Officer Group". 1990.
7. PHS Commissioned Corps *Distinguished Service Medal*. "For Outstanding contributions to the health of the Nation". 1991.
8. PHS Commissioned Corps *Surgeon General's Exemplary Service Medal*, from Surgeon General, Dr. Novello, "For continued development and implementation of the Research Officer Group for doctoral level researchers in the Corps". 1992.
9. PHS Commissioned Corps *Surgeon General's Medallion*, from Surgeon General, Dr. Novello, "For outstanding leadership, exemplary performance, and extraordinary support to the Office of the Surgeon General and the United States Public Health Service". 1993.
10. U.S. Department of Health and Human Services, Public Health Service, NIH, Special Act Award, In recognition and Appreciation of Sustained High Quality Work Performance. 1994.

Positions Held in Scientific Societies and Journals:

1. Elected to the Scientific Board of the *Fund for Integrative Biomedical Research*, 1980-1984.
2. Appointed to the Editorial Board of the Journal *Electrophoresis*, December 1984-1988.
3. Elected to International and National Councils of the *Electrophoresis Society*, 1984-1987.
4. Elected President of the *International Electrophoresis Society* January 1, 1986 to March 21, 1991.
5. Elected President of the *American Electrophoresis Society* June 1, 1986 to June 1, 1989.
6. Elected Senior Associate Editor of the Journal: *Electrophoresis*, September 14, 1986 to January 1, 1988.

7. Appointed to the Board of Editors, *Analytical Biochemistry* 1987 to the present.
8. Elected Editor-In-chief of *Applied and Theoretical Electrophoresis*, 1988 to 1996.
9. Appointed to the Editorial Board of the Journal: *BioTechniques*, 1992 to 2001
10. Appointed to the Board of Editors, *Insight* 1998 to the present.
11. Appointed to the Alzheimer's disease Association's Initial Review Board of the Medical and Scientific Advisory Council 1998 to the present.

Non-Federal Funding Awards:

1. Awarded funds from the Glenn Foundation for Medical Research for support of a Research Fellow, 1981-1984.
2. Awarded funds from the Yarbrough Foundation for Medical Research, for the support of two post-doctoral fellows, 1984-1986.
3. Established CRADA with Monoclonetics, Houston, Texas, to study plasma protein variations in disease states, . This CRADA supported one computer scientist, one post-doctoral fellow and a technician, 1989 - 1999
4. Established CRADA with Abbott Laboratories, Chicago, IL., to study cerebrospinal fluid protein variations in disease states, This CRADA supported two technicians, 1990-1994.
5. Established CRADA with Molecular Geriatrics, Chicago, Ill., to develop therapies for Alzheimer's diseases and other related neurodegenerative diseases. This CRADA supported one computer scientist, and three post-doctoral fellows. 1992-1995.
6. Established CRADA with Exponential Biotherapies, Inc., New York, NY, to develop technologically enhanced bacteriophage therapy for bacterial infections that involve the CNS as well as non-CNS tissue. This CRADA supported one post-doctoral fellow and one technician. 1994 - 1999.

Current Commercial Affiliations:

Member of Scientific advisory board of Panacea Pharmaceuticals Inc.

Member of the Board and one of the Founders of Hygea Pharmaceuticals Inc.

Bibliography

July 17, 2006

Name: Carl R. Merrill, M.D.

Scientist Emeritus, NIH

BIBLIOGRAPHY

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- [14] 5,721,100 Three highly informative microsatellite repeat polymorphic DNA markers, Polymeropoulos,M. and Merrill,C.R. [1998].

- [15] 5,766,892 Antibacterial therapy with bacteriophage genotypically modified to delay inactivation by the host defense system together with an antibiotic, Merrill, C.R., Carlton,R.M., and Adhya,S. [1998].
- [16] 5,811,093 Bacteriophage Lambda genotypically modified to delay inactivation by the host defense system, Merrill, C.R., Carlton,R.M., and Adhya,S. [1998].
- [17] 5,817,797 Sequencing DNA: A Modification of the Polymerase Chain Reaction, L.G. Mitchell and Merrill,C.R. [2000]
- [18] 6,740,492 High sensitivity phage display biomolecule detection, Merrill, C.R. [2004]

Patents Pending:

- [19] Direct use of tissue to isolate anti-HDS modified phage, Merrill, C.R., Carlton,R.M., and Adhya,S. [U.S. Serial No.], reference numbers: P8026-5015.
- [20] Therapeutic use of phage expressing toxin-binding and /or cytokine-binding proteins, Merrill, C.R., Carlton,R.M., and Adhya,S. reference numbers: V108026-09004
- [21] Depletion of lysogeny genes and toxin genes from bacteriophage use in the epidemiologic control of bacterial illness, Merrill, C.R., Carlton,R.M., and Adhya,S. [U.S. Serial No.], reference numbers: V108026-09005.
- [22] Bacteriophage having multiple host range, Merrill, C.R., Scholl,D. and Adhya,S. reference numbers: NIH205.001PR
- [23] Reporter Bacteriophage to Determine Sensitivity of a Clinical Bacterial Isolate to a Therapeutic Bacteriophage, Merrill, C.R., Scholl,D. and Adhya,S.
- [24] *Trans*-Splicing Mediated Photodynamic Therapy, Mitchell, L.G., Otto,E. and Merrill, C.R.

Invited Lectures:

- 1. "Bacterial Gene Expression in Mammalian Cells," at the *Workshop on Mechanisms and Prospects of Genetic Exchange*, Berlin, December, 1971.
- 2. "Bacterial Gene Expression in Mammalian Cells," in the *Debye Lecture Series at the E.I.Du Pont De Nemours and Company*, Delaware, March, 1971.
- 3. "Effects of Bacteriophage on Eukaryotes," at the *Sixth International Symposium on Molecular Biology, Johns Hopkins School of Medicine*, Baltimore, MD, 1972.
- 4. "Transduction in Mammalian Cells," at the *Fourth International Conference on Birth Defects*, Vienna, Austria, September, 1973.
- 5. Invited participant in: *Conference on Genetic Recombination Hazards*, Asilomar, CA, 1975.
- 6. "Interactions of Bacterial Viruses and Bacterial Genes with Animal Systems," at the *Molecular Genetic Modification of Eucaryotes Symposium*, University of Minnesota, 1977.

7. "Quantitative Two-Dimensional Electrophoresis as a Screen for Genetic Disease Markers," *Third International Conference on Electrophoresis*, Charleston, SC, 1981.
8. Organized and served as co-chairman of Conference on Alzheimer's Disease, Down's syndrome and Aging, sponsored by The Kroc Foundation (proceedings published by the New York Academy of Sciences), 1981.
9. Invited to plan and participate as a speaker at the *Fourth International Conference on Electrophoresis*, Athens, Greece, April, 1982.
10. "Quantitative Two-Dimensional Electrophoresis for Studies of Inborn Errors of Metabolism," at the: *Clinical Applications and Developments in Two-Dimensional Electrophoresis Symposium*, Mayo Clinic, Rochester, MN, November, 1981.
11. "Genetics, Forensics, and Electrophoresis" at the *International Symposium on the Forensic Applications of Electrophoresis* at the Forensic Science Research and Training Center, The FBI Academy, Quantico Va. 1984.
12. "Analysis of electrophoretograms", at the *European Molecular Biology Laboratory*, Heidelberg, Germany, March 1986.
13. "Protein Detection" to the *Joint Meeting of the British Electrophoresis Society and the Techniques group of the Biochemical Society*, Oxford University, England, July 17, 1985.
14. "Silver Stain Detection of Proteins" at the *American Chemical Society symposium on "New Directions in Electrophoretic Methods"* at the National Meeting of the American Chemical Society, Sept. 13-18, 1985.
15. "Protein detection" at the 1986 *Meeting of the American Branch of the Electrophoresis Society*, sponsored by the National Bureau of Standards and the Electrophoresis Society, March 26, 1986.
16. "Development and Application of Silver Stains for Electrophoresis" at the *2nd Joint meeting of the American and Japanese Histochemical Societies*, June 9-13, 1986.
17. "Recent Advances and Applications in the Art and Science of Detecting Proteins and Nucleic Acids by Silver Staining" at the 5th *Meeting of the International Electrophoresis Society*, London, September 9-12, 1986.
18. "Strategies for the use of protein databases to examine disease processes", Banbury Center, Cold Spring Harbor Laboratory, New York, May 10-12, 1987.
19. "Silver Staining to Aid Understanding Complex Biological Systems" at the International Conference on Gold and Silver in Medicine, Bethesda, Maryland, May 13-15, 1987.
20. "Mitochondrial DNA" at the *DNA Technology in Forensic Science Symposium* at the Forensic Science Research and Training Center, The FBI Academy, Quantico Va. May 31-June 2, 1988.
21. "Mechanisms and Applications of Protein Detection by Silver Staining" at *Electrophoresis'88, Sixth Meeting of the International Electrophoresis Society*, Copenhagen Denmark, 4th-7th July 1988.
22. "Silver Staining" in: *Clinical Applications of Electrophoresis*, Vienna, Austria, November 8-11, 1988.

23. "Molecular strategies for the study of diseases with genotypic heterogeneity" *American College of Neuropsychopharmacology*, San Juan, December 11, 1988.
24. "Clinical Applications of Electrophoresis and protein databases", for the *Federation of European Biological Societies*, in Aarhus Denmark May, 1989.
25. "Advances in Forensic Applications of Mitochondrial DNA" at the *DNA Technology in Forensic Science Symposium* at the Forensic Science Research and Training Center, The FBI Academy, Quantico Va. June, 1989
26. "New Methods of High Resolution Protein Electrophoresis - Clinical Applications", at: the *American Electrophoresis Society meeting on Electrophoretic Techniques in Molecular Biology*, Washington D.C. July, 1989.
27. "Diseases and the Mitochondrial Genome", *Natl. Institute of Neurol. Diseases, Grand Rounds*, NIH, Bethesda Md. January, 1990.
28. Opening Address, *International Electrophoresis Society*, Washington D.C. March 1991.
29. "High Resolution Protein Electrophoresis, High Sensitivity Protein Detection and Clinical Applications," *Abbott Laboratories Symposium on Protein Isolation and Characterization*, Abbott Park, Illinois, August 1991.
30. "Inheritance of Schizophrenia and Components of the Schizophrenic Syndrome: Findings to Date and Future Prospects for Biochemical Genetic Markers", *NIH Research Festival'91*, September 1991.
31. "Molecular Basis for Neuropsychiatric diseases: A balance between DNA and Protein Approaches", *Abbott Laboratory Distinguished Scientist Speakers Forum*. Abbott Park, Illinois, December 1991.
32. "Effect of Neuroleptic Drugs on Cerebrospinal Fluid Proteins," *American College of Neuropsychopharmacology*, San Juan, December 1991.
33. "Search for Diagnostic markers and understanding in diseases of unknown etiology affecting the central nervous system". *Electrophoresis Society*, Research Triangle Park, North Carolina, June 1992.
34. "Chairman, session on: High resolution protein databases and the genome" and lecture on: The clinical applications of two-dimensional electrophoresis in diseases affecting the central nervous system". *International Council of Electrophoretic Societies, ELPHO '93*, Sandefjord, Norway, June 1993.
35. Invited to present: "Mitochondrial deletions in the human central nervous system in aging and disease states". *Third Berkshire Neuroscience Symposium*, June 1994.
36. Invited to Chair session on High resolution protein electrophoretic databases, and to speak on: Acute phase plasma proteins in disease states. *Symposium on Clinical Applications of High Resolution Two Dimensional Electrophoresis*, Siena Italy, September 1994.
37. "Development of a relational database for the quantitative and qualitative comparison of body fluid proteins in normal and disease states". *Electrophoresis Society*, Rockville, Maryland, March 1995.

38. "Is there a relationship between hypoxia and brain mitochondrial DNA deletions?". *Neurodegenerative Diseases '95: Molecular and Cellular Mechanisms and Therapeutic Advances*, Washington, DC, May 1995.
39. "Use of 2d protein electrophoresis in the development of antibacterial agents". *Symposium on "From Genome To Proteome: 2nd Siena 2D electrophoresis meeting"* Siena Italy, September 1996.
40. "A perspective on the development of silver staining detection of proteins and nucleic acids". *Electrophoresis '97, International Council of Electrophoresis Societies '97*, Seattle, Washington, March 1997.
41. "Potential of Bacteriophage as antibacterial therapy" *FDA CBER*, Bethesda, MD, April 1997.
42. "Development of Long-circulating phage as potential antibacterial therapeutic agents" *Structural Biology Interest Group, NIH*, Bethesda, MD, March 1998,
43. "Protein Alterations in Neurodegenerative Diseases", *The 1998 Manhattan Alzheimers Disease Conference*, Manhattan, NY, March 1998
44. "Development of phage therapy for 21st Century Medicine", *Intenational Phage Meeting*, Olympia, Washington, July 1998.
45. "Advances in the use of bacteriophage to treat antibiotic resistant Infections", *Frontiers in Biomedicine, George Washington University Medical Center Grand Rounds and HELIX web site, Washington D.C.*, January 1999.
46. "A new single molecule protein detection system", *Electrophoresis in Medicine, Annual meeting of the Electrophoresis Society, Bethesda, MD*, August 1999.
47. "New approaches for the detection of proteins," *Pierce Chemical Company, Rockford, ILL.* Jan 2000
48. "Phage as an Antibacterial Agent", *British Broadcasting System Lecture* February 2000
49. "Bacteriophage as antibacterial agents" *Invited lecture, Department of Biology, Catholic University of America, Washington, D.C.* Feb 2000
50. "Protein Detection by Exponential Amplification". *in Symposium on "From Genome To Proteome: 4nd Siena 2D electrophoresis meeting"* Siena Italy, September 2000.
51. "Use of Exponential Amplification of phage for detection of proteins" *Invited lecture, "Third Annual Phage Display Technologies symposium"* Cambridge, Massachusetts, April 2001
52. "Studies of protein changes in diseases affecting the Nervous system and the need for greater sensitivity of protein detection" *Invited lecture in symposium on: "Current 2-D separation technologies applied to the study of complex protein mixtures"*, Frederick, Maryland July 2001
53. "Use of Phage in antibacterial therapy", *lecture in symposium on: " Bacteriophage at the NIH: An early genetic model expands disease treatment and diagnosis.* NIH, Bethesda MD October 2001
54. "Phage Therapy: potential and problems", *FDA,CEBR, Bethesda, MD*, March 2002.

55. "Phage interactions with mammalian systems: pharmacokinetic effects and other considerations for antibacterial phage therapy" Invited lecture, at symposium on Phage Therapy – Potential and Challenges" The Banbury Center, Cold Spring Harbor Laboratory, New York, November 2002.
56. "The Plasma proteome, perspectives associated with polymorphisms, normalization and effects of disease states" Invited lecture, at "First Annual Human Proteome Organization (HUPO) Congress", Versailles, France November 2002.
57. "Bioterrorism and Biotechnology: Anticipating Future Threats and Countermeasures" Invited participant, National Research Council, Virginia, January 2003
58. "Phage antibacterial therapy", Invited lecture, Department of Microbiology at North Carolina State University, Raleigh, North Carolina, March 2003.
59. "Can Bacteriophage be developed into a Reliable Antibacterial Agent?" 2003 Harold C Neu Infectious Diseases Conference, San Francisco, California, April 2003
60. "Phage Therapy in Experimental Infectious Disease Models" Invited Lecture, "American Society for Microbiology, 103rd General Meeting, Washington, DC. May 2003
61. "Bacteriophage workshop", Invited Participant, for the Advanced Systems Concepts Office (ASCO) of the Defense Threat Reduction Agency (DTRA) Alexandria, Virginia, May 2004
62. Invited Chair for session "Phage in therapeutics and biotechnology" at the "American Society for Microbiology Conference, The New Phage Biology, Key Biscayne, Florida, August 2004
63. "Developments needed for Phage Therapy" Invited Lecture, "American Society for Microbiology Conference, The New Phage Biology, Key Biscayne, Florida, August 2004

Cooperative Research And Development Agreements(CRADA) Established:

1. Psychoneurodiagnostic Markers in Cerebrospinal Fluid, established with Abbott Laboratory, 1990 to 1994.
2. Development of diagnostic markers from serum and plasma protein high resolution two dimensional electrophoretic pattern, established with Monoclonetics Inc., 1989 to 1999
3. Development of therapies for Alzheimer's disease and diseases associated with deletions in the mitochondrial genome. Molecular Geriatrics Inc., 1992 to 1995.
4. Development of new approaches for the use of bacterial viruses in the treatment of infectious disease. Exponential BioTherapies., 1994 to 1999